

Application No. 09/840,146

Docket No. 11245/46604

AMENDMENTS TO THE CLAIMS

Claims 1-35 (cancelled).

36. (Currently amended) A method of inhibiting growth of a refractory tumor that has failed or been resistant to treatment comprising administering to ~~a human~~ an epidermal growth factor receptor (EGFR) antagonist and a chemotherapeutic agent to a human having a refractory tumor that has failed or been resistant to treatment with an antineoplastic, wherein administration is effective to inhibit growth of the refractory tumor.

37. (Previously added) The method according to claim 36, wherein the refractory tumor overexpresses EGFR.

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38. (Previously added) The method according to claim 36, wherein the refractory tumor is a refractory tumor of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, or liver.

39. (Previously added) The method according to claim 36, wherein the refractory tumor is a refractory tumor of the colon or head and neck.

40. (Previously added) The method according to claim 36, wherein the refractory tumor is a refractory squamous cell tumor.

41. (Previously added) The method according to claim 36, wherein the EGFR antagonist is administered intravenously.

42. (Previously added) The method according to claim 36, wherein the EGFR antagonist is administered orally.

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43. (Previously added) The method according to claim 36, wherein the EGFR antagonist is administered prior to administration of the chemotherapeutic agent.

44. (Previously added) The method according to claim 36, wherein the EGFR antagonist is administered at a dose of about 10 to about 500 mg/m² weekly.

45. (Previously added) The method according to claim 36, wherein the EGFR antagonist inhibits stimulation of EGFR by its ligand.

46. (Previously added) The method according to claim 45, wherein the EGFR antagonist inhibits binding of EGFR to its ligand.

47. (Previously added) The method according to claim 45, wherein the EGFR antagonist binds EGFR externally.

48. (Currently amended) The method according to claim 5945, wherein the EGFR antagonist binds EGFR internally.

49. (Currently amended) The method according to claim 5945, wherein the EGFR antagonist inhibits binding of ATP to EGFR.

50. (Currently amended) The method according to claim 5945, wherein the EGFR antagonist competes with ATP for EGFR.

51. (Previously added) The method according to claim 45, wherein the EGFR antagonist inhibits EGFR phosphorylation.

52. (Previously added) The method according to claim 45, wherein the EGFR antagonist inhibits EGFR tyrosine kinase activity.

53. (Currently amended) The method according to claim 36, wherein the EGFR antagonist comprises an antibody, or ~~functional equivalent~~ fragment thereof, specific for EGFR.

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54. (Previously added) The method according to claim 53, wherein the antibody comprises a constant region of a human antibody.

55. (Previously added) The method according to claim 54, wherein the antibody is a chimeric antibody comprising a variable region of a mouse antibody.

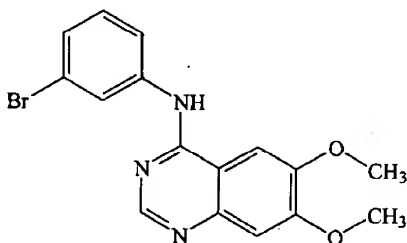
56. (Previously added) The method according to claim 54, wherein the antibody is a humanized antibody comprising a variable region having complementarity-determining regions (CDRs) of a mouse antibody and framework regions of a human antibody.

57. (Previously added) The method according to claim 54, wherein the antibody is a human antibody comprising a variable region of a human antibody.

58. (Currently amended) The method according to claim 54, wherein the antibody, or fragment thereof, is administered at a dose sufficient to saturate EGFR.

59. (Withdrawn) The method according to claim 36, wherein the EGFR antagonist comprises a small molecule, wherein the small molecule has a molecular weight of less than or about 450.

60. (Withdrawn) The method according to claim 59, wherein the small molecule comprises a compound, PD 153035, having the following structure:

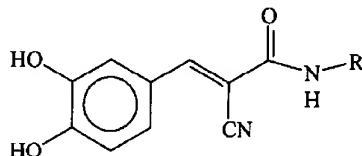


61. (Withdrawn) The method according to claim 59, wherein the small molecule comprises a benzylidene malononitrile or tyrphostin compound.

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62. (Withdrawn) The method according to claim 61, wherein the benzylidene malononitrile compound comprises the following structure:



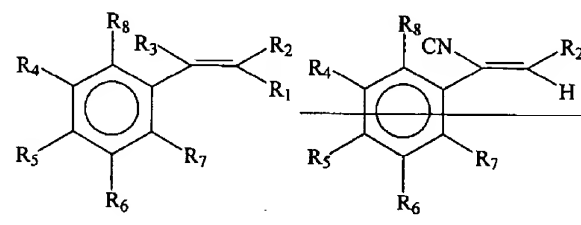
wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH₃.

63. (Withdrawn) The method according to claim 59, wherein the small molecule comprises a styryl substituted heteroaryl compound.

64. (Withdrawn) The method according to claim 63, wherein the styryl substituted heteroaryl compound comprises a monocyclic ring with 1 or 2 heteroatoms or a bicyclic ring with from 1 to about 4 heteroatoms, which can be optionally substituted or polysubstituted.

Cl
H

65. (Currently amended, withdrawn) The method according to claim 63, wherein the styryl substituted heteroaryl compound comprises the following structure:

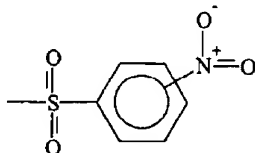


wherein R is H, alkyl, or aralkyl; R₂ is an about 8- to about 12-membered bicyclic aryl ring including 1 to about 4 N, O or S atoms or 1 to about 4 N-oxide groups, which ring can be optionally substituted with 1 to about 3 R₉ substituents having no common points of attachment to said ring; R₄, R₅, R₆, R₇, and R₈ are each independently H, CN, alkyl, halo, OR, CHO, COOH, NRR or an N-oxide thereof, NO₂, NHCOCH₃, SR, CF₃,

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CH=CHCOOH, CHCO(CH₂)₂COOH, heterocyclic, heteroaryl; each R₉ is independently alkyl, CN, halo, OR, CHO, COOH, NRR, or an N-oxide thereof, NO₂, NHCOCH₃, SR, CF₃, CH=CHCOOH, NHCO(CH₂)₂COOH, heterocyclic or heteroaryl, or the following structure:

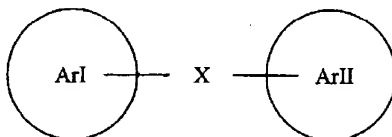


66. (Withdrawn) The method according to claim 59, wherein the small molecule comprises a tricyclic pyrimidine compound.

67. (Withdrawn) The method according to claim 66, wherein the tricyclic pyrimidine compound comprises a 4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine; 4-(3-bromoanilino)-8-nitrobenzothieno[3,2-d]pyrimidine; 8-amino-4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine or 4-(3-bromoanilino)-8-methoxybenzothieno[3,2-d]pyrimidine.

68. (Withdrawn) The method according to claim 59, wherein the small molecule comprises a bis mono or bicyclic aryl, heteroaryl, carbocyclic, or heterocarbocyclic compound.

69. (Currently amended, withdrawn) The method according to claim 59, wherein the small molecule comprises a compound having the following structure:



wherein ArI and ArII are independently a substituted or unsubstituted mono- or bicyclic ring, said rings optionally substituted with 0 to about 3 R groups; X is (CHR₁)₀₋₄ or

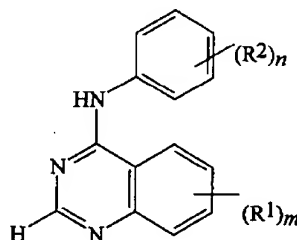
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$(\text{CHR}_1)_m\text{-Z-(CHR}_1)_n$, which Z is O, NR' , S, SO, or SO_2 , m and n are 0-3 and $m+n=0-3$ and R_1 and R' are independently H or alkyl, or a pharmaceutically acceptable salt thereof.

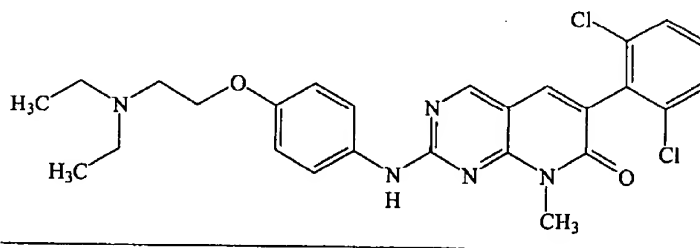
70. (Withdrawn) The method according to claim 59, wherein the small molecule comprises a quinazoline derivative.

71. (Withdrawn) The method according to claim 70, wherein the quinazoline derivative comprises a compound having the following structure:



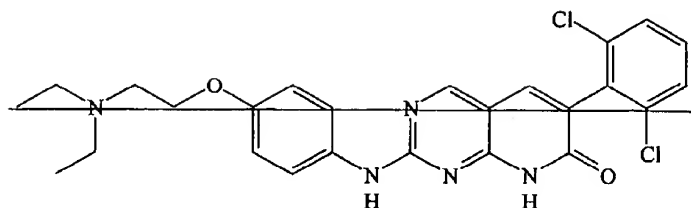
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uf
wherein m is 1, 2 or 3 and each R^1 includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkylenedioxy and n is 1 or 2 and each R^2 includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically acceptable salt thereof.

72. (Currently amended, withdrawn) The method according to claim 59, wherein the small molecule comprises a compound, PD 166285, having the following structure:



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73. (Previously added) The method according to claim 36, wherein the chemotherapeutic agent comprises amifostine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozocin, cyclophosphamide, carmustine, lomustine, doxorubicin, doxorubicin lipo, gemcitabine, daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin, paclitaxel, docetaxel, aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-11, 10-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, interferon alpha, interferon beta, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, or chlorambucil or a combination thereof.

74. (Previously added) The method according to claim 36, wherein the chemotherapeutic agent comprises cisplatin, doxorubicin, paclitaxel, Irinotecan (CPT-11), or topotecan, or a combination thereof.

75. (Previously added) The method according to claim 36, wherein the chemotherapeutic agent is administered at a dose of about 69 to about 125 mg/m² weekly.

76. (Previously added) The method according to claim 36, wherein the method further comprises administering an adjuvant.

Claims 77-125 (withdrawn).

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¹²⁵
~~126.~~ (Previously added) The method according to claim 122, wherein the chemotherapeutic agent is administered at a dose of about 69 to about 125 mg/m² weekly.

¹²⁶
~~127.~~ (Currently amended) A method of inhibiting growth of a head and neck squamous cell refractory tumor that has failed or been resistant to treatment comprising administering to ~~a human~~ a chimeric antibody that is specific for epidermal growth factor receptor (EGFR) and cisplatin to a human having a head and neck squamous cell refractory tumor that has failed or been resistant to treatment with an antineoplastic, wherein administration is effective to inhibit growth of the head and neck squamous cell refractory tumor.

¹²⁷ new?
~~128.~~ (Currently amended) A method of inhibiting growth of a refractory tumor of the colon that has failed or been resistant to treatment comprising administering to ~~a human~~ a chimeric antibody that is specific for epidermal growth factor receptor (EGFR) at a loading dose of about 400 mg/m² and Irinotecan (CPT-11) to a human having a refractory tumor of the colon that has failed or been resistant to treatment with an antineoplastic, wherein administration is effective to inhibit growth of the refractory tumor of the colon.

¹²⁸
~~129.~~ (New) The method of claim ¹²⁶~~127~~, wherein the chimeric antibody is administered at a loading dose of about 100 mg/m².

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~~130.~~ (New) The method of claim ¹²⁶~~127~~, wherein the chimeric antibody is administered at a loading dose of about 400 mg/m².

¹³⁰
~~131.~~ (New) The method of claim ¹²⁶~~127~~, wherein the chimeric antibody is administered at a loading dose of about 500 mg/m².

¹³¹
~~132.~~ (New) The method of claim ¹²⁴~~127~~, wherein the chimeric antibody is administered at a weekly dose of about 100 mg/m².

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132¹²⁶ ~~133.~~ (New) The method of claim ~~127~~¹²⁶, wherein the chimeric antibody is administered at a weekly dose of about 250 mg/m².

133¹²⁶ ~~134.~~ (New) The method of claim ~~127~~¹²⁶, wherein the cisplatin is administered at a weekly dose of about 100 mg/m².

134¹²⁷ ~~135.~~ (New) The method of claim ~~128~~¹²⁷, wherein the chimeric antibody is administered at a weekly dose of about 250 mg/m².

135¹³⁴ ~~136.~~ (New) The method of claim ~~135~~¹³⁴, wherein the Irinotecan (CPT-11) is administered at weekly dose of about 125 mg/m².

136¹³⁷ ~~137.~~ (New) The method of claim 53, wherein the EGFR antagonist is administered at a loading dose of about 400 mg/m².

137¹³⁸ ~~138.~~ (New) The method of claim 53, wherein the EGFR antagonist is administered at a weekly dose of about 250 mg/m².

138¹³⁹ ~~139.~~ (New) The method of claim 75, wherein the chemotherapeutic agent is administered at a dose of about 125 mg/m² weekly.
